

WHAT IS CLAIMED IS:

1 1. A method of improving a phenotypic defect in a cell that contains a
2 conformationally defective target protein wherein the conformational defect causes the
3 phenotype defect, comprising contacting a first cell that expresses said conformationally
4 defective target protein with an amount of a protein stabilizing agent that is effective to
5 improve the conformational defect, thereby improving the phenotypic defect of the first
6 cell in comparison with a second cell having the same conformationally defective target
7 protein and phenotypic defect, wherein the second cell is not contacted with a protein
8 stabilizing agent; wherein Congo Red is not the protein stabilizing agent.

1 2. A method according to claim 1, wherein the cell is selected from the group
2 of cells consisting of bacterial and eukaryotic cells.

1 3. A method according to claim 1, wherein the defective target protein is the
2 gene product of a naturally occurring mutant nucleic acid.

1 4. A method according to claim 1, wherein the defective target protein is the
2 gene product of a heterologous nucleic acid.

1 5. A method according to claim 1, wherein the defective target protein is
2 selected from the group consisting of the cystic fibrosis transmembrane conductance
3 regulator (CFTR) protein, emphysema and chronic liver disease α -1 anti-trypsin inhibitor,
4 LDL receptor (familial hypercholesterolemia), β -hexylaminidase (Tay-sachs), fibrillin
5 (Martan syndrome), superoxide dismutase (amyotrophic lateral sclerosis), collagen
6 (scurvy) α -ketoacid dehydrogenase complex (maple syrup urine disease), p53 (cancer),
7 type I procollagen pro- α (osteogenesis imperfecta), β -amyloid (Alzheimer's disease),
8 crystallins (cataracts), rhodopsin (retinitis pigmentosa), and insulin receptor
9 (leprechaunism).

1 6. A method according to claim 1, wherein the reference protein stabilizing
2 agent is selected from the group consisting of dimethylsulfoxide (DMSO), deuterated
3 water, polyols, sugars, and amino acids and derivatives thereof.

1 7. The method according to claim 6, wherein the protein stabilizing agent is
2 selected from the group consisting of glycerol, erythritol, trehalose isofluoroside, sorbitol,
3 and polyethylene glycol.

1 8. The method according to claim 6, wherein the protein stabilizing agent is
2 selected from the group consisting of glycine, alanine, proline, taurine, betaine, octopine,
3 glutamate, sarcosine, gamma-aminobutyric acid, and trimethylamine N-oxide (TMAO).

1 9. A method according to claim 1, wherein the phenotypic defect is caused
2 by a condition selected from the group consisting of improper folding, improper co- and
3 post-translational modification, improper subcellular targeting, inability to bind biological
4 ligands, aggregation, proteolytic degradation, and any combination thereof.

1 10. A method according to claim 9, wherein the condition that causes the
2 phenotypic defect occurs in a part of the protein that is selected from the group consisting
3 of pre-sequence, pro-sequence, and mature protein sequence.

1 11. A screening method for detecting a phenotypically defective cell whose
2 phenotypic defect is due to the presence of a conformationally defective target protein,
3 comprising the steps of
4 contacting a test cell having a phenotypic defect with a protein stabilizing agent,
5 and
6 determining whether such contact is effective to improve the phenotypic defect of
7 the cell.

1 12. A method according to claim 11, wherein the reference protein stabilizing
2 agent is selected from the group consisting of dimethylsulfoxide (DMSO), deuterated
3 water, polyols, and amino acids and derivatives thereof.

1 13. A method according to claim 9, wherein the cell is selected from the group
2 of cells consisting of bacterial and eukaryotic cells, in particular yeast, insect and
3 mammalian cells.

1 14. A method according to claim 11, wherein the defective target protein is the
2 gene product of a heterologous nucleic acid.

1 15. A method according to claim 11, wherein the defective target protein is
2 selected from the group wherein the defective target protein is selected from the group
3 consisting of the cystic fibrosis transmembrane conductance regulator (CFTR) protein,
4 emphysema and chronic liver disease α -1 anti-trypsin inhibitor, LDL receptor (familial
5 hypercholesterolemia), β -hexosaminidase (Tay-sachs), fibrillin (Marfan syndrome),
6 superoxide dismutase (amyotrophic lateral sclerosis), collagen (scurvy) α -ketoacid
7 dehydrogenase complex (maple syrup urine disease), p53 (cancer), type I procollagen
8 pro- α (osteogenesis imperfecta), β -amyloid (Alzheimer's disease), crystallins (cataracts),
9 rhodopsin (retinitis pigmentosa), and insulin receptor (leprechaunism).

1 16. A method of detecting the relative proportions of PrP^C and PrP^{Sc} present in
2 a composition, comprising:

3 mixing a composition that comprises prion proteins with a solution wherein only
4 one form, either PrP^C or PrP^{Sc}, is insoluble;
5 separating the form of PrP that is soluble from the form that is insoluble; and
6 determining the relative amounts of soluble and insoluble PrP.

1 17. A method according to claim 16, wherein the PrP is mixed with a solution
2 comprising about 1% Triton X-100 and about 1% DOC at 4 °C.

1 18. A method according to claim 16, wherein the soluble and insoluble forms
2 of PrP are separated by centrifugation.

1 19. The use of a protein stabilizing agent to improve a phenotypic defect in a
2 cell that contains a conformationally defective target protein wherein the conformational
3 defect causes the phenotype defect, wherein the protein stabilizing agent is selected from
4 the group consisting of dimethylsulfoxide (DMSO), deuterated water, polyols; and amino
5 acids and derivatives thereof.

1 20. A use according to claim 19, wherein the polyol is selected from the group
2 consisting of glycerol, erythritol, trehalose isofluoride; polyethylene glycol; and
3 sorbitol.

1 21. A use according to claim 20, wherein the amino acid or derivative thereof
2 is selected from the group consisting of glycine, alanine, proline, taurine, betaine,

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3 octopine, glutamate, sarcosine, gamma-aminobutyric acid, and trimethylamine N-oxide
4 (TMAO).

1 22. A use according to claim 19, wherein the defective target protein is
2 selected from the group consisting of the cystic fibrosis transmembrane conductance
3 regulator (CFTR) protein, emphysema and chronic liver disease α -1 anti-trypsin inhibitor,
4 LDL receptor (familial hypercholesterolemia), β -hexosaminidase (Tay-sachs), fibrillin
5 (Marfan syndrome), superoxide dismutase (amyotrophic lateral sclerosis), collagen
6 (scurvy), α -ketoacid dehydrogenase complex (maple syrup urine disease), p53 (cancer),
7 type I procollagen pro- α (osteogenesis imperfecta), β -amyloid (Alzheimer's disease),
8 crystallins (cataracts), rhodopsin (retinitis pigmentosa), and insulin receptor
9 (leprechaunism).